

# Bypassing agent prophylaxis in people with hemophilia A or B with inhibitors

## Review information

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### Dates

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### What's new

Date	Event	Description
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### History

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## Abstract

### Background

People with hemophilia A or B with inhibitors are at high risk of bleeding complications. Infusion of bypassing agents, such as recombinant activated FVII (rFVIIa) and plasma-derived activated prothrombin complex concentrate, are suggested as alternative therapies to factor VIII (haemophilia A) or IX (haemophilia B) for individuals who no longer respond to these treatments because they develop inhibitory antibodies. The ultimate goal of treatment is to preserve the individual's joints, otherwise destroyed by recurrent bleeds.

### Objectives

To assess the effects of bypassing agent prophylaxis to prevent bleeding in people with hemophilia A or B and inhibitors.

### Search methods

We searched for relevant studies from the Cystic Fibrosis and Genetic Disorders Group's Coagulopathies Trials Register, comprising of references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings. We also searched trial registries (16 February 2017) and bibliographic references of retrieved studies were reviewed for potential articles to be included in the review.

Date of the last search of the Cochrane Cystic Fibrosis and Genetic Disorders Coagulopathies Trials Register: 12 December 2016.

### Selection criteria

We included randomized and quasi-randomized controlled studies (cross-over or parallel design) evaluating the effect of

prophylaxis treatment with bypassing agents compared with on-demand treatment, or studies evaluating the effects of high-dose compared with low-dose prophylaxis in males of any age with hemophilia with inhibitors.

## Data collection and analysis

Two authors independently selected studies and extracted data and assessed the risk of bias according to standard Cochrane criteria. They assessed the quality of the evidence using the GRADE criteria.

## Main results

We included four randomized studies (duration 7 to 15 months) involving 116 males. Risk of bias was judged to be high in two studies due to the open-label study design and in one study due to attrition bias.

Two studies compared on-demand treatment to prophylaxis with bypassing agents. In one study (34 males) prophylaxis significantly reduced mean overall bleeding rates, MD - 7.27 (95% CI -9.92 to -4.62) (low quality evidence), mean number of overall bleeding events per month, MD -1.10 (95% CI -1.54 to -0.66), mean number of hemarthrosis, MD -6.60 (95% CI -9.32 to -3.88) (low quality evidence) and mean number of joints that had hemarthrosis, MD -0.90 (95% CI -1.36 to -0.44). The meta-analysis did not conclusively demonstrate significant benefit of prophylaxis on health-related quality of life as measured by Haem-A-QoL score, EQ-5D total score and utility score, EQ-5D VAS and SF-36 physical summary and mental summary score (low quality evidence for all health-related quality of life analyses).

The remaining two studies compared dose regimens. The results from one study (22 males) did not conclusively demonstrate benefit or harm of high-dose versus low-dose recombinant activated factor VIIa (rFVIIa) as a prophylaxis for overall bleeding rate, MD -0.82 (95% CI -2.27 to 0.63) (moderate quality evidence), target joint bleeding rate, MD -3.20 (95% CI -7.23 to 0.83) (moderate quality evidence) and serious adverse events, RR 9.00 (95% CI, 0.54 to 149.50) (moderate quality evidence).

The overall quality of evidence was moderate to low due to imprecision from limited information provided by studies with small sample sizes and incomplete outcome data in one study.

## Authors' conclusions

The evidence suggests that prophylaxis with bypassing agents may be effective in reducing bleeding in males with hemophilia with inhibitors. However, there is a lack of evidence for the superiority of one agent over the other or for the optimum dosage regimen. Further studies are needed to evaluate the benefits and harms of prophylaxis treatment on health-related quality of life, as well as the effects of dose of bypassing agents on the outcomes.

## Plain language summary

### The use of bypassing agents for preventing bleeding in people with hemophilia with inhibitors

#### Background

Infusion of bypassing agents, such as recombinant activated FVII (rFVIIa) and plasma-derived activated prothrombin complex concentrate (APCC), are suggested as alternative therapies to factor VIII (haemophilia A) or IX (haemophilia B) for individuals who no longer respond to these treatments because they develop inhibitory antibodies. The ultimate goal of treatment is to preserve the individual's joints, otherwise destroyed by recurrent bleeds. We therefore evaluated the effectiveness and safety of bypassing agents when used to prevent, as compared to treat, bleeds. We also compared different doses of bypassing agents in men with hemophilia A or B with inhibitors as a preventative (prophylactic) therapy.

#### Search date

The evidence is current to 12 December 2016.

#### Study characteristics

We searched the scientific databases for clinical studies evaluating the effects of bypassing agents in men with hemophilia A or B with inhibitors. We included four studies (duration 7 to 15 months), involving 116 individuals. Two studies compared the prophylactic infusion with bypassing agent to on-demand treatment (treatment given only after the bleeding occurred) and two studies compared high-dose to low-dose preventative therapies.

#### Key Results

Limited evidence showed that prophylactic use of bypassing agents reduced bleeding events, joint bleeding events and number of affected joints. There was no evidence for improved quality of life amongst those who received prophylaxis as compared to those who received on-demand therapy. There was no evidence for a difference in benefits or harms between high- and low-dose rFVIIa for prophylaxis.

#### Quality of evidence

The overall quality of evidence of these studies was moderate to low as the included studies were small and provided limited information. Also, in one of the studies, up to 24% of the men recruited were not included in the analysis of the results, which further increases imprecision of results.

## Background

### Description of the condition

Congenital deficiency of factor (F) VIII or FIX results in the formation of alloantibodies which inhibit the activity of infused

clotting factor concentrates (CFCs) in approximately 30% of people with severe (defined as less than 1 international unit (IU) dL<sup>-1</sup> baseline clotting factor activity) hemophilia A (FVIII deficiency) and 2% to 5% of those with severe hemophilia B (FIX deficiency) ([lorio 2010a](#)).

In an analysis of the UK Haemophilia Centre Doctors' Organisation database, the cumulative risk of inhibitor formation was 16% and 36% at five years and 75 years of age (respectively) for the 6078 males with hemophilia A and 6% and 8% (respectively) for the 1172 males with hemophilia B ([Darby 2004](#)). The rate of inhibitor formation is dependent on the residual or baseline circulating FVIII or FIX level, being greatest in those people with severe disease ([Hay 1998](#)). Among people with non-severe disease, those with certain mutations, particularly in the A2 and C2 domains of the F8 gene, are more likely to develop inhibitory antibodies.

Development of inhibitors is a complex process, but likely includes factors related to the individual being treated, the environment and the treatment provided. Patient-related or genetically determined factors include ethnicity, race, the severity of the hemophilia, hemophilia causing mutation, major histocompatibility class, and immunogenotype ([Astermark 2010a](#)). Environmental or non-genetic factors are ones perceived by the immune system as danger signals ([Matzinger 1994](#); [Matzinger 2012](#)) and may include the reason for the first infusion at a young age and the intensity of treatment ([Astermark 2010b](#)).

### Description of the intervention

Once the diagnosis of an inhibitor is made, treatment options include the management of acute bleeding, prevention of bleeding, and immune tolerance induction (ITI), the latter being the primary treatment option ([Collins 2013](#)). One randomized prospective trial of ITI in children with favorable risk factors has been completed ([Hay 2012](#)). Although 70% of participants had a complete response to ITI, six of 37 participants relapsed after a median of 9.5 months. Those in whom ITI failed or who relapsed after successful ITI, along with those in whom ITI was not attempted or those on ITI but still with bleeding, remain at risk for bleeding and hence are candidates for prophylaxis with a bypassing agent.

Recombinant activated FVII (rFVIIa) and plasma-derived activated prothrombin complex concentrate (APCC) are currently the only two bypassing agents available for use in people with hemophilia with inhibitors. Two randomized trials of acute bleeding management with bypassing agents have been completed, one with rFVIIa ([Young 2008](#)) and one with APCC ([Astermark 2007](#)) but neither involved a comparison of the prophylactic use of the two drugs. These trials were reviewed in 2010 and superiority of one treatment over the other in terms of hemostatic control or thrombosis risk could not be demonstrated in participants with acute bleeding ([lorio 2010b](#)). Similarly, several non-randomized studies failed to demonstrate superiority of one agent over the other ([Chuansumrit 2000](#); [Kavakli 2006](#); [Lusher 1998](#); [Pruthi 2007](#); [Santagostino 2006](#); [Seremetis 1994](#); [Shapiro 1998](#)).

Frequent bleeding, especially joint bleeding, is a common disease manifestation in people with hemophilia and inhibitors and impacts overall health, joint health, and quality of life ([Scalone 2006](#)). Prophylaxis is the use of treatment on a regular basis to prevent or reduce bleeding episodes. The choice of prophylactic infusion requires the medication to be effective for bleeding management. Therefore, prophylaxis in people with hemophilia with inhibitors that do not respond to routine factor concentrates must rely on the use of bypassing agents. In people without inhibitors, prophylaxis is regarded as standard of care and is associated with a reduction in musculoskeletal disease burden and with a good quality of life ([lorio 2011](#)). However, experience with prophylaxis is limited in people with inhibitors.

In 2013, Collins recommended that prophylaxis with a bypassing agent should be considered in children with inhibitors after the first hemarthrosis in an effort to prevent joint damage and in older people with recurrent bleeding ([Collins 2013](#)). Regarding the choice of bypassing agent, it was recommended that this decision be individualized based on prior response to treatment, logistics of administration and cost. In October 2013, the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation recommended that prophylaxis with bypassing agents should be considered in people with inhibitors ([MASAC 2013](#)). No specific guidelines were provided to guide clinicians who wished to prescribe prophylaxis.

The optimal treatment for people with hemophilia without inhibitors is the prophylactic administration of factor VIII (hemophilia A) or factor IX (hemophilia B) concentrates ([lorio 2011](#)). The development of neutralizing antibodies makes treatment of bleeding with CFCs more difficult and when the concentration of the antibody is above a certain level ( $\geq 5$  Bethesda units dL<sup>-1</sup> (BU)), replacement therapy is no longer effective ([Berntorp 2006](#)). In these cases with high titres of antibody, treatment with bypassing agents, either rFVIIa or APCC, is necessary to control acute bleeding ([Shapiro 2003](#)).

Prevention of bleeding or prophylaxis in cases with high titres of antibody requires use of rFVIIa or APCC.

### How the intervention might work

The development of anti-factor VIII or anti-factor IX antibodies makes the administration of substitution therapy with factor VIII or IX (respectively) ineffective. Bypassing agents are treatments that are able to activate the coagulation cascade independently of factor VIII and IX; thus they are unaffected by the presence of factor VIII or factor IX inhibitors. Bypassing agents, including rFVIIa and APCC, have different mechanisms of action by which they drive coagulation. It is known that rFVIIa activates factor Xa on an activated platelet surface or when, it is bound to tissue factor, it can directly activate thrombin. Alternatively, APCC mainly acts by providing factors IX and X which are able to bypass the need for FVIII to drive thrombin generation ([Hedner 2000](#)).

Prophylaxis with bypassing agents may prevent bleeding in people with hemophilia with inhibitors and specifically reduce overall bleeding rates and joint bleeding rates without excess thrombotic and infectious risks. Ideally, prophylaxis with

bypassing agents in people with inhibitors will ensure long-term joint protection, in the way that the prophylactic administration of factor VIII and IX does in people without inhibitors.

### Why it is important to do this review

The rationale for this review is that prophylaxis with bypassing agents may improve the quality of life for people with hemophilia A or B with inhibitors and reduce the economic burden of treatment. This information may help to inform and guide clinicians in decision making when managing people with congenital hemophilia and inhibitors.

## Objectives

To assess the effects of bypassing agent prophylaxis to prevent bleeding in people with hemophilia A or B and inhibitors.

## Methods

### Criteria for considering studies for this review

#### Types of studies

Randomized controlled studies and quasi-randomized controlled studies (cross-over or parallel design).

#### Types of participants

Males of any age with severe congenital hemophilia A or B complicated by high-responding inhibitors to FVIII or FIX, respectively, requiring a bypassing agent as prophylaxis to control or prevent bleeding.

#### Types of interventions

Prophylaxis, at any dose, any dosing frequency, and any regimen, of rFVIIa or APCC for preventing bleeding versus each other or no prophylaxis.

#### Types of outcome measures

##### Primary outcomes

1. Overall bleeding events (per month), as defined by study authors

##### Secondary outcomes

1. Annualised bleeding rate
2. Target joint bleeding rate
3. Annualised joint bleeding rate (AJBR)
4. Quality of life (QoL) (generic and specific validated scales including EQ-5D, Haem-A-QoL, Haemo-QoL)
5. Safety of the bypassing agents including adverse events, serious adverse events, or thromboembolic events
6. Cost and resource utilization when comparing prophylaxis to on-demand treatment regimens, including overall drug utilization

### Search methods for identification of studies

There were no restrictions regarding language or publication status.

#### Electronic searches

We identified relevant studies from the Cystic Fibrosis and Genetic Disorders Group's Coagulopathies Trials Register using the terms: (Factor VIII Inhibitors) OR (factor inhibitors).

The Coagulopathies Register was compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), weekly searches of MEDLINE and prospective hand-searching of one specialized journal, *Haemophilia*. Unpublished work was identified by searching the abstract books of five major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the International Society of Haemostasis and Thrombosis Congresses; and the International Congresses of World Federation of Haemophilia. For full details of all searching activities for the register, please see the relevant section of the *Cochrane Cystic Fibrosis and Genetic Disorders Group's website*.

Date of the last search of the Cochrane Cystic Fibrosis and Genetic Disorders Coagulopathies Trials Register: 12 December 2016.

We also searched trial registries such as ClinicalTrials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) and the International Clinical Trials Registry Platform ([www.who.int/ictpr/en/](http://www.who.int/ictpr/en/)) in an attempt to identify relevant studies for inclusion ([Appendix 1](#)). Date of most recent search: 16 February 2017.

#### Searching other resources

The bibliographic references of retrieved studies were reviewed for additional references to be included in this review.

### Data collection and analysis

#### Selection of studies

Two review authors independently reviewed the abstracts from the identified articles to select those that were potentially

eligible to be included in the review. The authors retrieved the full text reports of studies that were deemed potentially relevant and linked together multiple reports of the same study. The authors independently examined the full text of the studies for compliance with the eligibility criteria; and if necessary contacted the study investigators to determine study eligibility. The authors resolved any disagreements on study inclusion by discussion in order to reach a consensus.

### **Data extraction and management**

A pair of authors (CC, SJN and MS) independently reviewed the identified articles and extracted data on the following (a third author arbitrated any differences).

1. Inclusion criteria for the study
2. Location and timeframe of the study
3. Participant number and demographics
4. Study methods
5. Study design
6. Type, characteristics and duration of the intervention and control groups if applicable
7. Outcome measures and description
8. Information on limitations or bias (or both)

### **Assessment of risk of bias in included studies**

A pair of authors (CC, SJN and MS) independently assessed the risk of bias of the included studies. The risk of bias was assessed using Cochrane's tool for assessing the risk of bias according to the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)). For each study, the risk of bias was noted as being either 'high risk', 'low risk', or 'unclear risk' for the following criteria.

1. Sequence generation
2. Allocation concealment
3. Blinding of participant and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selected outcome reporting
7. Other issues

### **Measures of treatment effect**

For the primary outcome, overall bleeding events were represented as a mean number of bleeding events per month. Secondary outcomes of target joint bleeding events and annualised joint bleeding events were represented as a mean number of bleeding events per month. We analyzed the data as continuous data, and reported mean differences (MD) with the corresponding 95% confidence intervals (CIs).

For safety outcomes, i.e. adverse events related to treatment, the effect was presented as the proportion of males presenting the event, and a risk ratio (RR). We calculated a pooled estimate of the treatment effect for each outcome using the pooled RR and 95% CIs.

With respect to health-related quality of life (HRQoL), the mean and standard deviation (SD) of scores from scales were presented. We calculated the mean change from baseline for each group or the mean post-intervention values and SD for each group. We converted standard errors (SE) to SDs. We produced a pooled estimate of treatment effect by calculating the MD and 95% CIs. If economic data are reported in updates of this review, we will analyse these data in the same way.

If for a future update, continuous scores measure the same outcome but in a variety of ways (e.g. different scales to measure knowledge or quality of life), we plan to standardize the outcomes to a uniform scale using the standardized MD (SMD).

Where studies reported multiple measures for the same outcome, the review authors considered absolute changes in the measure in the context of comparable data being available for each participant before and after the intervention (i.e. change from baseline). The authors recorded continuous data, such as joint score change, as either mean change from baseline for each group or mean post-treatment values (if change from baseline was not reported) and SD for each group.

### **Unit of analysis issues**

No cluster-randomized studies were identified. If cluster-randomized studies are identified for updates of the review, we will check these studies for unit of analysis errors and perform analysis based on the advice given in chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011b](#)).

When conducting a meta-analysis combining results from cross-over studies, we used the methods recommended by Elbourne ([Elbourne 2002](#)). We extracted (or calculated) MDs and SEs adjusted for the paired design of cross-over studies. If this had not been possible, we would have considered whether data were presented by treatment period and include only first-period data in the analysis. If neither of these options were possible, we would have included data from cross-over studies narratively in the review.

We included one cross-over study in the review ([Leissinger 2011](#)). For the outcome of overall bleeding events, we were able to extract individual participant data from a graph and calculate a MD and adjusted SE. We were also able to estimate that the correlation between treatment arms was around 0.4 from these data. Therefore, we have used this correlation estimate to adjust estimates of SE for other continuous outcomes measured in this study.

### **Dealing with missing data**



If reports were incomplete, we attempted to contact the original investigators in an effort to obtain the necessary data or information. Where the original investigators could not provide additional information, we examined the proportion and distribution of missing data (e.g. proportion of missing outcome data, demographic data, missing information regarding study design methods etc.). We also considered, where possible, whether data were likely to be missing at random or not and whether the missing data were likely to have had an impact on the results of the study. We judged the risk of bias due to incomplete outcome data accordingly and performed sensitivity analyses, excluding studies with large proportions of missing data, if appropriate.

### **Assessment of heterogeneity**

We assessed heterogeneity through visual examination of the combined data presented in the forest plots, and by considering the  $I^2$  statistic together with  $\text{Chi}^2$  values (significance level  $P < 0.1$ ) ([Deeks 2011](#)). The  $I^2$  statistic reflects the likelihood that variation of results across studies are due to heterogeneity rather than by chance, and is interpreted as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

### **Assessment of reporting biases**

We intended to assess publication bias by constructing, then visually inspecting, the funnel plot (where a minimum of 10 studies could be included), and investigated outcome reporting bias by comparing the methods and results sections of the published papers.

### **Data synthesis**

Where meta-analysis could be conducted, we employed a fixed-effect model in the first instance. For future updates, when moderate or higher heterogeneity is identified ( $I^2$  of around 30% or higher), a random-effects model will be employed. For dichotomous outcomes (adverse events related to treatment), we employed the Mantel-Haenszel method of meta-analysis and present pooled RRs and 95% CIs. For continuous outcomes (overall bleeding events, annualised bleeding rate, target joint bleeding events, annualised bleeding events, HRQoL, economic data, joint score change), we employed the inverse variance method of meta-analysis and present pooled MD or SMD (as appropriate, see [Measures of treatment effect](#)) and 95% CIs.

### **Subgroup analysis and investigation of heterogeneity**

If we had identified moderate or higher heterogeneity ( $I^2$  of around 30% or higher), we intended to investigate this by subgroup analyses based on:

1. diagnosis (e.g. hemophilia A or B);
2. age of the participants (boys or adult males).

### **Sensitivity analysis**

We intended to explore the impact of including studies with high levels of missing data on the overall treatment effect, if appropriate.

### **Summary of findings and quality of the evidence (GRADE)**

In a post hoc change from protocol, we have presented a summary of findings tables for each comparison in the review ([Summary of findings table 1](#); [Summary of findings table 2](#)).

The following outcomes were reported in the tables (chosen based on relevance to clinicians and consumers): overall bleeding events; annualised bleeding rate; target joint bleeding rate; AJBR; quality of life; safety of the bypassing agents.

We determined the quality of the evidence using the GRADE approach; and downgraded evidence in the presence of a high risk of bias in at least one study, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results, high probability of publication bias. We downgraded evidence by one level if they considered the limitation to be serious and by two levels if very serious ([Balshem 2011](#); [Guyatt 2008](#)).

## **Results**

### **Description of studies**

#### **Results of the search**

See [Figure 1](#).

We identified 96 citations from the database searches. We identified a further 89 references from searches of trial registries. Of the total 185 references, we removed three duplicates. After we reviewed the remaining titles and abstracts, 151 were discarded as not being relevant and we retrieved the full-text references (where possible) of nine studies (31 references). Of these, four unique studies (reported in 26 references) were eligible randomized controlled studies and were included in the review ([Antunes 2014](#); [Konkle 2007](#); [Leissinger 2011](#); [Ljung 2013](#)). We excluded four studies ([NCT02622321](#); [NCT02795767](#); [NCT02847637](#); [NCT03020160](#)) and classified one study as awaiting further assessment ([NCT01105546](#)).

## Included studies

See [Characteristics of included studies](#).

Four studies are included in the review ([Antunes 2014](#); [Konkle 2007](#); [Leissinger 2011](#); [Ljung 2013](#)).

The Antunes study was a multicenter, parallel, randomized controlled study conducted in 17 centers ([Antunes 2014](#)). Participants were enrolled if they were hemophilia A or B with a history of high-titre inhibitor ( $> 5$  BU/mL) or low-titre inhibitor ( $\leq 5$  BU/mL) with refractory to increased dosing of factor replacement therapy. A total of 17 participants were randomized to prophylaxis group and 19 were randomized to the on-demand therapy group. Prophylaxis regimen was nanofiltered FVIII inhibitor bypassing activity (FEIBA NF) 85  $\pm$  15 units/kg bolus infusion every other day. Participants who were in the on-demand therapy group received FEIBA NF administration when they experienced a bleeding episode, dosing depended on type of bleeding. The study lasted for 12 months. The primary outcome was annualised bleeding rate. Secondary outcomes were AJBR, overall bleeding events, target joint bleeding events, occurrence of new target joints, hemostatic efficacy, total FEIBA NF utilization, safety and QoL.

The Konkle study was a multicenter, parallel, randomized controlled study conducted in 20 centers ([Konkle 2007](#)). Participants were enrolled if they had severe hemophilia A or B with a high inhibitor titre ( $> 2$  BU/mL), required treatment of bleeds with a bypassing agent and had had at least four bleeds requiring hemostatic drug treatment within the previous month prior to enrolling. There were three study periods (pre-prophylaxis, prophylaxis and post-prophylaxis). Each period was for three consecutive months. Eleven participants were randomized to rFVIIa 270  $\mu$ g/kg once daily and 11 were randomized to rFVIIa 90  $\mu$ g/kg once daily. The primary outcome was the number of bleeds per month. Secondary outcomes were site-specific bleeding rates, safety, HRQoL and orthopedic joint scores.

The Leissinger study was a multicenter, cross-over study conducted in 16 centers ([Leissinger 2011](#)). Eligible participants were males with severe hemophilia A and a history of high-titre inhibitor ( $> 5$  BU/mL), who were older than two years of age, being treated with bypassing agents and had six or more episodes of bleeding requiring treatment in the six months prior to study enrollment. Prophylaxis regimen was anti-inhibitor coagulant complex (AICC)-FEIBA at a target dose of 85 ( $\pm$ 15%) units/kg. During the on-demand therapy period, participants received FEIBA at a dose of 85 ( $\pm$ 15%) units/kg if they experienced bleeding episodes. A total of 17 participants were randomized to prophylaxis first (six months of prophylaxis, followed by a three-month washout period and six months of an on-demand period). A total of 17 participants were randomized to on-demand therapy first (six months of on-demand therapy, followed by three months of washout period and six months of prophylaxis). The primary outcome was total bleeding events (prophylaxis versus on-demand periods). Secondary outcomes were the number of joint bleeds, the number of target joint bleeds, HRQoL and safety.

The Ljung study was a multicenter, parallel study conducted in 19 centers ([Ljung 2013](#)). Eligible participants had hemophilia A or B with high titre inhibitor ( $\geq 5$  BU/mL, frequent bleeds, age 12 to 65 years), had at least two bleeding episodes within the last month or 12 bleeding episodes within the last six months prior to enrolling. There were three study periods (three months of observation, followed by three months of prophylaxis and one month of observation). The prophylaxis regimen was 40K glycoPEGylated recombinant FVIIa bypassing agent (N7-GP) administered at target doses of 25  $\mu$ g/kg, 100  $\mu$ g/kg and 200  $\mu$ g/kg intravenously every second day. During the on-demand period, participants received rFVIIa for the treatment of bleeding episodes. The primary outcome was a reduction in the annualised bleeding rate (prophylaxis versus on-demand therapy periods). Secondary outcomes were the number of specific bleeds (stratified by sites) and causes of bleeding.

## Excluded studies

We identified four studies which were excluded from the review ([NCT02622321](#), [NCT02795767](#), [NCT02847637](#), [NCT03020160](#)) as the study drug was neither rFVIIa or APCC.

## Studies awaiting assessment

We identified one study which we are currently awaiting further information on, once obtained, we will assess this for eligibility ([NCT01105546](#)).

## Risk of bias in included studies

See [Figure 2](#) and [Figure 3](#).

### Allocation (selection bias)

The Antunes study used centralised stratified, block randomization ([Antunes 2014](#)), the Konkle study used centralised computer-generated randomization ([Konkle 2007](#)) and the Leissinger study conducted the randomization and treatment allocation by using centralized call center (telephone randomization) ([Leissinger 2011](#)). Risk of selection bias was judged as 'low risk' of bias for these three studies. The Ljung study described that the participants were randomized and stratified by age ([Ljung 2013](#)). There was no further information regarding random sequence generation and allocation concealment; the risk of bias for this study was judged as 'unclear'.

### Blinding (performance bias and detection bias)

Two studies were open-label and there was no information regarding the blinding of outcome assessors; therefore the risk of bias was judged as 'high risk' ([Antunes 2014](#); [Leissinger 2011](#)). The Konkle and Ljung studies described the blinding procedure as providing an equal volume of trial drug to be injected in both groups ([Konkle 2007](#); [Ljung 2013](#)). There was no information regarding blinding of the outcome assessors; the risk of bias was judged as 'low risk' for the latter studies.

### *Incomplete outcome data (attrition bias)*

The Antunes study reported that two participants withdrew from the on-demand group and one from the prophylaxis group ([Antunes 2014](#)). The Ljung study reported that three participants withdrew during the study period (one from the 100 µg/kg group and one from the 200 µg/kg group) ([Ljung 2013](#)). There were no withdrawals during the study period in the Konkle study ([Konkle 2007](#)). All participants were included in an intention-to-treat analysis. The participants were well balanced across groups. The risk of bias was judged to be 'low risk' for these three studies. The Leissingner study reported that one participant withdrew consent before receiving the study medication and a further seven did not complete the study; the risk of bias was judged as 'high risk' for this study ([Leissingner 2011](#)).

### *Selective reporting (reporting bias)*

All of the studies clearly specified primary and secondary outcomes. The data on all outcomes were reported. There was no evidence of selective reporting, therefore, the risk of bias was judged to be 'low risk' for all four studies.

### *Other potential sources of bias*

All four studies were deemed to be at 'low risk' of bias from other source of bias.

### *Effects of interventions*

Two comparisons were made in this review, prophylaxis compared to on-demand therapy and low-dose compared to high-dose therapy.

#### ***Prophylaxis compared to on-demand therapy***

Two studies recruiting 70 participants contributed to this comparison ([Antunes 2014](#); [Leissingner 2011](#)). Both studies compared prophylaxis to on-demand therapy with FEIBA (AICC or NF).

#### **Primary outcome**

##### **1. Overall bleeding rates (per month)**

One study reported on the bleeding rate per month (over a six-month period) on prophylaxis and on-demand therapy ([Leissingner 2011](#)). At six months, prophylaxis with bypassing agent (FEIBA) significantly reduced mean overall bleeding rates, MD -7.27 (95% CI -9.92 to -4.62) (low quality evidence) ([Analysis 1.1](#)) and the mean number of overall bleeding per month, MD -1.10 (95% CI -1.54 to -0.66) compared with those who are on-demand group ([Analysis 1.2](#)).

#### **Secondary outcomes**

##### **1. Annualised bleeding rates**

One study reported on annualised bleeding rates; however, data were presented as median values and cannot be entered into analysis ([Antunes 2014](#)). The median annualised bleeding rate was significantly lower among those who were allocated to prophylaxis as compared to on-demand treatment (7.9 versus 28.7) (moderate quality evidence).

##### **2. Joint bleeding rates**

One study reported mean number of hemarthrosis ([Leissingner 2011](#)). At six months, prophylaxis with bypassing agent (FEIBA) significantly reduced mean number of hemarthrosis, MD -6.60 (95% CI -9.32 to -3.88) when compared to on-demand treatment (low quality evidence) ([Analysis 1.3](#)). Mean number of joint hemorrhages was significantly lower among those who were on prophylaxis, MD -0.90 (95% CI -1.36 to -0.44) when compared to those with on-demand therapy ([Analysis 1.4](#)).

##### **3. AJBR**

One study reported on annualised bleeding rates; however, data were presented as median values and cannot be entered into analysis ([Antunes 2014](#)). The median AJBR was significantly lower among those who were allocated to prophylaxis as compared to on-demand treatment (6.0 versus 22.9) (moderate-quality evidence).

##### **4. Quality of life**

Two studies reported outcome regarding to HRQoL (low-quality evidence) ([Antunes 2014](#); [Leissingner 2011](#)). The Antunes study evaluated HRQoL using the Haem-A-QoL, Haemo-QoL, EQ-5D, and general pain visual analog scale (VAS) at six and 12 months ([Antunes 2014](#)). Leissingner assessed HRQoL using the EQ-5D questionnaire and the Short-Form (SF)-36 Health survey ([Leissingner 2011](#)).

After 12 months of study, mean change from baseline of Haem-A-QoL score was not significantly different but in favour of prophylaxis as compared with on-demand treatment, MD 3.40 (95% CI, -5.53 to 12.33) ([Analysis 1.5](#)). Mean change from baseline of EQ-5D scores were not significantly different but in favour prophylaxis, measuring at six months, MD 0.09 (95% CI -0.09 to 0.27) and 12 months, MD 0.07 (95% CI -0.13 to 0.27) ([Analysis 1.6](#)). Mean change from baseline of EQ-5D VAS was not significantly different but in favour prophylaxis, measuring at six months, MD 4.11 (95% CI, -3.66 to 11.88) and 12 months, MD 9.90 (95% CI, -5.93 to 25.73) ([Analysis 1.7](#)). Mean change from baseline of EQ-5D utility score were not statistically different between prophylaxis and on-demand group, MD 0.00 (95% CI -0.12 to 0.12) ([Analysis 1.8](#)). The mean change from baseline of SF36-physical summary score was not significantly different comparing between prophylaxis and on-demand treatment at six months, MD 2.90 (95% CI -1.53 to 7.33) ([Analysis 1.17](#)). Likewise, the mean change from baseline of SF36-mental summary score was not significantly different comparing between prophylaxis and on-demand treatment at six months, MD



1.20 (95% CI -2.75 to 5.15) ([Analysis 1.18](#)). There were also no significant differences between the treatments for any of the individual SF-36 physical or mental domains ([Analysis 1.9](#); [Analysis 1.10](#); [Analysis 1.11](#); [Analysis 1.12](#); [Analysis 1.13](#); [Analysis 1.14](#); [Analysis 1.15](#); [Analysis 1.16](#)).

## 5. Safety of the bypassing agents

Two studies reported on the safety of the bypassing agents (low quality evidence) ([Antunes 2014](#); [Leissinger 2011](#)). Antunes reported 36 (28.8%) of treated participants in two groups experienced serious adverse effects ([Antunes 2014](#)). No study reported thromboembolic events or major safety issues. Leissinger reported that one participant had an allergic reaction to the study drug during prophylaxis and three participants had events related to central venous access during prophylaxis and on-demand therapy ([Leissinger 2011](#)).

## 6. Cost and resource utilization

Neither study reported this outcome ([Antunes 2014](#); [Leissinger 2011](#))

### *High-dose compared to low-dose prophylaxis therapy*

Two studies recruiting 46 participants contributed to this comparison ([Konkle 2007](#); [Ljung 2013](#)). Both compared doses of rFVIIa; Konkle compared 270 µg/kg to 90 µg/kg and Ljung compared three doses of 200 µg/kg, 100 µg/kg and 25 µg/kg ([Konkle 2007](#); [Ljung 2013](#)).

#### Primary outcome

##### 1. Overall bleeding rate (per month)

One study reported the overall bleeding rates comparing high-dose (270 µg/kg) versus low-dose (90 µg/kg) rFVIIa ([Konkle 2007](#)). High-dose rFVIIa reduced the mean number of bleeds per month when compared to low-dose rFVIIa, but the difference between the groups was not statistically significant, MD -0.82 (95% CI -2.27 to 0.63) (moderate quality evidence) ([Analysis 2.1](#)).

Ljung reported the mean annualised bleeding rate per month, comparing three doses of rFVIIa (200 µg/kg, 100 µg/kg and 25 µg/kg) ([Ljung 2013](#)). The mean annualised bleeding rates per month were reduced during prophylaxis as compared to the on-demand treatment period for all three doses of rFVIIa. The bleeding rate could not be analysed between the groups due to the inadequate outcome reports.

#### Secondary outcomes

##### 1. Annualised bleeding rates

Ljung reported annualised bleeding among those who received three different doses of rFVIIa ([Ljung 2013](#)). As compared to on-demand treatment period, the annualised bleeding rate during prophylaxis were reduced by 36%, 45% and 52% in participants who received rFVIIa 200 µg/kg, 100 µg/kg and 25 µg/kg, respectively. The bleeding rate could not be analysed between the groups due to the inadequate outcome reports.

##### 2. Joint bleeding rate

One study reported target joint bleeding rates comparing high-dose (270 µg/kg) versus low-dose (90 µg/kg) rFVIIa ([Konkle 2007](#)). At three months, high-dose rFVIIa reduced mean joint bleeding rates when compared to low-dose rFVIIa but the difference between the groups was not statistically significant, MD -3.20 (95% CI -7.23 to 0.83) (moderate quality evidence) ([Analysis 2.2](#)).

##### 3. AJBR

Neither study reported this outcome ([Konkle 2007](#); [Ljung 2013](#)).

##### 4. Quality of life

Neither study reported this outcome ([Konkle 2007](#); [Ljung 2013](#)).

## 5. Safety of the bypassing agents

Two studies reported adverse events comparing high-dose versus low-dose rFVIIa ([Ljung 2013](#); [Konkle 2007](#)). There was no statistical difference of the risk of adverse events between doses, RR 1.00 (95% CI 0.57 to 1.76) for 200 µg/kg compared to 100 µg/kg, RR 1.50 (95% CI 0.67 to 3.34) for 200 µg/kg compared to 25 µg/kg, RR 1.50 (95% CI 0.67 to 3.34) for 100 µg/kg compared to 25 µg/kg and RR 0.89 (95% CI 0.56 to 1.40) for 270 µg/kg compared to 90 µg/kg (moderate-quality evidence) ([Analysis 2.3](#)).

One study reported serious adverse events comparing high-dose versus low-dose rFVIIa ([Konkle 2007](#)). Four participants who received high-dose rFVIIa (270 µg/kg) reported serious adverse events compared to no participants who received low-dose (90 µg/kg). However, this difference between groups was not statistically significant, RR 9.00 (95% CI 0.54 to 149.50) ([Analysis 2.4](#)).

## 6. Cost and resource utilization

Neither study reported this outcome ([Konkle 2007](#); [Ljung 2013](#))

## Discussion

### Summary of main results

Four studies were found to be eligible for the review ([Antunes 2014](#); [Konkle 2007](#); [Leissinger 2011](#); [Ljung 2013](#)).

Two studies compared prophylaxis versus on-demand treatment ([Antunes 2014](#); [Leissinger 2011](#)) and two studies compared high to low doses of bypassing agents for prophylaxis ([Konkle 2007](#); [Ljung 2013](#)). The main findings of this Cochrane Review and meta-analysis in people with hemophilia with inhibitors suggested that prophylaxis with bypassing agents reduces overall bleeding rates and joint bleeding rates as compared to on-demand treatment. No statistically significant differences in change from baseline for HRQoL were found and this review did not conclusively rule out benefit or harm of high-dose compared with low-dose rFVIIa.

### Overall completeness and applicability of evidence

All of the included studies enrolled people with hemophilia A or hemophilia B with inhibitors. Two studies compared prophylaxis with on-demand treatment ([Antunes 2014](#); [Leissinger 2011](#)). However, the remaining two studies did not include participants who were given on-demand treatment as a control ([Konkle 2007](#); [Ljung 2013](#)). The prophylactic durations ranged from three months to 12 months. The data were presented differently (e.g. crude bleeding rate, annualised bleeding rate or bleeding per month) and reported in mean or median. Consequently, meta-analyses were prevented in some cases. Two studies evaluated HRQoL; however, the tools used in these studies varied ([Antunes 2014](#); [Leissinger 2011](#)). Consequently, a pooled analysis could not be performed for the majority of HRQoL domains. Although we observed statistically significant differences of the clinical outcomes regarding to the reduction of overall bleeding rates and joint bleeding rates in those who were allocated to prophylaxis as compared to on-demand treatment, the clinical relevance of this finding warrant further prospective studies with a greater number of participants and a longer duration of follow-up.

Although the studies included in this review were conducted as multicenter, multinational studies; bypassing agents as a prophylaxis in people with hemophilia with inhibitors are not widely used in countries where the resources are limited. Hence, the applicability of this evidence to certain groups of people with hemophilia A or B is limited.

### Quality of the evidence

When comparing between prophylaxis versus on-demand treatment, the quality of the evidence was moderate for outcomes relating to annualised bleeding rates; we downgraded the evidence due to the imprecision of limited data from one or two small studies. Other outcomes (bleeding rates, HRQoL and safety) provided low quality evidence for this comparison; in addition to imprecision, evidence was also downgraded due to incomplete outcome data with up to 24% of participants excluded from one cross-over study.

When comparing high-dose to low-dose rFVIIa, the quality of evidence was moderate for overall bleeding rates, target joint bleeding rate and safety of bypassing agents; we downgraded evidence due to imprecision of limited data from one or two small studies. Other outcomes were not reported for this comparison.

### Potential biases in the review process

We performed extensive searches for this Cochrane Review. The methodology regarding study selection, data extraction, risk of bias assessment and analyses were rigorously conducted. We contacted the corresponding authors for clarification on data; however, there were some missing reported outcomes regarding overall bleeding rate, joint bleeding rate and health-related outcomes. In addition, the small number of included studies in this review precluded us from conducting subgroup analyses.

### Agreements and disagreements with other studies or reviews

Valentino conducted a systematic review of six observational studies, involving 34 hemophilia people with inhibitors who were treated with FEIBA for prophylaxis ([Valentino 2010](#)). The median prophylactic dose was 78.5 unit per kg. There was 63.9% reduction in overall bleeding events and 73% reduction in annual joint bleeding.

## Authors' conclusions

### Implications for practice

The evidence suggests that prophylaxis with bypassing agent may be effective in people with hemophilia A or B with inhibitors for the reduction of overall bleeding rates and joint bleeding rates (low to moderate quality evidence). There is insufficient evidence to show that prophylaxis does affect health-related quality of life (HRQoL) as compared to on-demand treatment (low quality evidence). There is lack of evidence of superiority of one agent over the other as well as the dosage regimen.

### Implications for research

The small sample sizes and substantial attrition rates of the included studies limited the precision of the effect estimates. Larger prospective studies are warranted in order to evaluate the efficacy of prophylaxis compared to on-demand treatment and high-dose versus low-dose regimen of bypassing agents. In addition, outcome measures (such as bleeding event and HRQoL) were non-uniformly reported. Consequently, it is difficult to compare the results across the studies and to perform meta-analyses. Hemophilia-specific tools for assessing HRQoL may be more informative and uniform. The hemophilia research community needs to develop a consensus on measuring and reporting outcomes in hemophilia-related literature.

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## Contributions of authors

Chatree Chai-Adisaksopha assessed eligibility of studies, performed data extraction and risk of bias assessment, interpreted analyses, constructed the summary of findings tables and drafted the review text.

Sarah Nevitt performed data extraction and risk of bias assessment, performed and interpreted analyses and assisted with construction of summary of findings tables and drafting of the review text.

Mindy Simpson drafted the original protocol, assessed eligibility of studies, performed data extraction, assessed risk of bias assessment and commented on the final draft version.

Maissaa Janbain commented on the final draft version.

Barbara Konkle commented on the final draft version.

## Declarations of interest

**Chatree Chai-Adisaksopha (lead author):** none known.

**Sarah Nevitt (co-author):** none known.

**Mindy Simpson (co-author):** has been compensated for participation in advisory boards by Baxter Bioscience (now Shire), Biogen Idec (now Bioverativ), CSL Behring, NovoNordisk, Grifols, and Octapharma. Rush University Medical Center receives grant support on behalf of Mindy Simpson from CSL Behring, NovoNordisk, Biogen (now Bioverativ) and Baxter Bioscience (now Shire).

**Maissaa Janbain (co-author):** once received consultant fees from CSL Behring and Bayer for attending advisory board meetings.

**Barbara Konkle (co-author):** receives research support from Baxter Bioscience, Biogen-Idec, and Novo-Nordisk and has consulted for Baxter Bioscience, Bayer, Biogen-Idec, CSL-Behring, Novo-Nordisk and Pfizer.

## Differences between protocol and review

In a post hoc change from protocol, two summary of findings tables (one for each comparison) have been added to the review. Outcomes were selected based on relevance to clinicians and consumers

## Published notes

Sarah J Nolan (author of the protocol) is now Sarah J Nevitt.

## Characteristics of studies

### Characteristics of included studies

*Antunes 2014*

<b>Methods</b>	Multicenter parallel randomized study conducted in 17 centres in Bulgaria, Russia, Croatia, Poland, Romania, USA, Japan and Brazil
<b>Participants</b>	<p>36 males (prophylaxis (n = 17) or on-demand therapy (n = 19))</p> <p>Inclusion criteria: hemophilia A or B with documented history of high-titre inhibitor (&gt; 5 BU/mL) or low-titre inhibitor (≤ 5 BU/mL) refractory to increased dosing of either FVIII or FIX for at least 12 months; were ≥ 4 and ≤ 65 years of age; were currently being treated on demand with bypassing agents; had ≥ 12 bleeding episodes in the previous 12 months; and a negative HIV status, or if positive, with a stable CD4 count</p> <p>Exclusion criteria: symptomatic liver disease; had platelet count &lt; 100,000 per µL; were currently receiving ITI or prophylaxis; needed elective surgery; needed alpha-interferon or protease inhibitor use; or had previous thromboembolic events</p>
<b>Interventions</b>	<p>Prophylaxis: FEIBA NF 85 +/- 15 units/kg intravenously bolus infusion every other day</p> <p>On demand: FEIBA NF, dosing depended on type of bleeding and was at discretion of the investigator</p> <p>Duration of treatment: 12 months (+/- 14 days)</p>
<b>Outcomes</b>	<p>Primary outcome: annualised bleeding rate</p> <p>Secondary outcomes: AJBR, overall bleeding events, target joint bleeding events, occurrence of new target joints, hemostatic efficacy, total FEIBA NF utilization, safety and quality of life</p>
<b>Notes</b>	Study sponsored by Baxter Healthcare Corporation

## Risk of bias table

<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Block randomization in a 1:1 ratio with stratification by geography (block size not stated)
Allocation concealment (selection bias)	Low risk	The randomization scheme was centralized
Blinding of participants and personnel (performance bias)	High risk	Open-label study
Blinding of outcome assessment (detection bias)	High risk	Open-label study
Incomplete outcome data (attrition bias)	Low risk	2 participants withdrew from on-demand group (1 serious adverse event and 1 surgery) and 1 from the prophylaxis group (adverse event). Withdrawal rate similar across groups and all participants included in an ITT analysis
Selective reporting (reporting bias)	Low risk	No protocol available. All outcomes defined in the methods reported in the results, no evidence of selective reporting
Other bias	Low risk	None identified

Konkle 2007



<b>Methods</b>	Multicenter randomized parallel study conducted across 20 sites in Argentina, Brazil, Bulgaria, the Philippines, Poland, Romania, Russia, South Africa, Spain, Turkey and USA
<b>Participants</b>	<p>22 participants (rFVIIa 270 µg/kg (n = 11) and rFVIIa 90 µg/kg (n = 11))</p> <p>Inclusion criteria: males with severe congenital hemophilia A or B with a high documented history of inhibitor titre (with an inhibitor titre &gt; 2 BU/mL in the preceding 12 months), a requirement for current treatment of bleeds with bypassing agents, and at least four bleeds requiring hemostatic drug treatment (except dental bleeds and bruises) within the previous month.</p> <p>Exclusion criteria: prophylaxis with any hemostatic drug within the last 3 months, ITI within the last month, known pseudotumours, platelet count &lt; 50,000 per µL, advanced atherosclerotic disease, and congenital or acquired coagulation disorders other than hemophilia A or B</p>
<b>Interventions</b>	<p>There were 3 phases of 3-month study period (pre-prophylaxis, prophylaxis and post-prophylaxis periods).</p> <p>Prophylaxis with high dose: activated rFVIIa 270 µg/kg once daily, slow bolus intravenously over a period of 2 minutes</p> <p>Prophylaxis with low dose: rFVIIa 90 µg/kg once daily</p>
<b>Outcomes</b>	<p>Primary outcome: number of bleeds per month comparing between during the prophylaxis period and pre-prophylaxis period</p> <p>Secondary outcomes: number of bleeds per month comparing between post-prophylaxis period and prophylaxis period, site specific bleeding rates, safety, HRQoL, orthopedic joint scores</p>
<b>Notes</b>	<p>On-demand treatments of acute/breakthrough bleeds were continued as normal practice throughout the study. 38 participants were originally recruited for the study, 37 entered the pre-treatment observation period but 15 were withdrawn</p> <p>Study sponsored by Novo Nordisk</p>

## Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralized computer-generated randomization list was used to randomly allocate participants
Allocation concealment (selection bias)	Low risk	Centralized computer-generated randomization list was used to randomly allocate participants
Blinding of participants and personnel (performance bias)	Low risk	Blinding was maintained by providing an equal volume of study drug to be injected in both groups
Blinding of outcome assessment (detection bias)	Unclear risk	No information provided
Incomplete outcome data (attrition bias)	Low risk	No withdrawals during the study period. All randomized participants analysed, ITT approach used
Selective reporting (reporting bias)	Low risk	No protocol available. All outcome defined in the methods mentioned in the results, some outcomes reported in more detail than others (e.g. no numerical results reported for orthopedic status)
Other bias	Low risk	None identified

<b>Methods</b>	Multicenter randomized cross-over study conducted at 16 centres in Europe and USA
<b>Participants</b>	<p>34 participants</p> <p>Inclusion criteria: severe hemophilia A and a history of a factor VIII inhibitor titre exceeding 5 BU, older than 2 years old, being treated with bypassing agents and had 6 or more episodes of bleeding requiring treatment in the 6 months before the study</p> <p>Exclusion criteria: receiving immune tolerance therapy, regular prophylaxis with any hemostatic agent, symptomatic liver disease, platelet count of less than 100,000 per <math>\mu\text{L}</math>, planned elective surgery within 12 months, used an investigational product within 1 month of study enrolment, planned to begin treatment with interferon or protease inhibitor</p>
<b>Interventions</b>	<p>Prophylaxis: AICC (FEIBA) administration at a target dose of 85 units/kg (+/- 15%) on 3 non-consecutive days weekly</p> <p>On demand: AICC at a target dose of 85 units/kg (+/- 15%) for bleeding episode</p> <p>Duration of treatment: 6 months of prophylaxis, 3 months of washout period and 6 months of on-demand therapy (prophylaxis first), 6 months of on-demand therapy, 3 months of washout period and 6 months of prophylaxis (on-demand therapy first)</p>
<b>Outcomes</b>	<p>Primary outcome: reduction of bleeding events during prophylaxis period compared with the on-demand period</p> <p>Secondary outcomes: number of joint bleeding, number of target joint bleeding, HRQoL and safety</p>
<b>Notes</b>	Study funded by Baxter Bioscience who provided AICC. Study investigators and a medical writer paid by Baxter Bioscience prepared the manuscript

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization conducted from a centralized call center (telephone randomization) – information from the online protocol
Allocation concealment (selection bias)	Low risk	Randomization conducted from a centralized call center (telephone randomization) – information from the online protocol
Blinding of participants and personnel (performance bias)	High risk	For ethical and practical reasons, participants were aware of study assignments
Blinding of outcome assessment (detection bias)	High risk	For ethical and practical reasons, participants were aware of study assignments
Incomplete outcome data (attrition bias)	High risk	Per protocol results reported for efficacy outcomes (reduction in bleeding rates / joint bleeding rates), ITT approach for safety outcomes (monthly hemorrhage rates, adverse effects).  Up to 24% of participants excluded from results: 1 patient withdrew consent before receiving study medication. The ITT group comprised 33 participants, of whom 7 did not complete the study: 1 withdrew because of an allergic reaction, 2 died, 1 was lost to follow-up after Hurricane Katrina, and 3 withdrew consent (2 during the on-demand period and 1 during the prophylaxis period)
Selective reporting (reporting bias)	Low risk	Online protocol available. All outcomes reported in protocol fully reported in the study, no evidence of selective reporting
Other bias	Low risk	None identified

**Ljung 2013**

Methods	Multicenter randomized parallel study conducted over 19 sites in France, Japan, Malaysia, Serbia, Sweden, Turkey, UK, USA, South Africa
Participants	24 participants (8 to each group but 1 not dosed)  Inclusion criteria: people with hemophilia A or B with high-responding inhibitors ( $\geq 5$ BU/mL) and frequent bleeds, age 12 - 65 years, at least 2 bleeding episodes within the last month or 12 bleeding episodes within the last 6 months  Exclusion criteria: low platelet count ( $< 50,000$ per $\mu\text{L}$ ), active pseudotumours, advanced atherosclerotic disease, severe liver disease, renal dysfunction, coagulation disorders other than congenital hemophilia or a history of thromboembolic events
Interventions	On-demand period: activated rFVIIa for the treatment of bleeding episodes  Prophylaxis period: 40K glycoPEGylated rFVIIa bypassing agent (N7-GP) administration at a target doses of 25, 100 and 200 $\mu\text{g/kg}$ intravenously over 2 - 5 minutes every second day  Duration of the study: 3 months of observation period (on-demand therapy), 3 months of prophylaxis period and 1 month of observation period
Outcomes	Primary outcome: reduction in annualised bleeding rate  Secondary outcome: number of specific bleeds stratified by sites and causes
Notes	Study sponsored by Novo Nordisk

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomized and stratified by age, no further information given regarding generation of random sequence
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias)	Low risk	Double-blind study: placebo solution was used to provide equal injection volume irrespective of dose
Blinding of outcome assessment (detection bias)	Unclear risk	No information provided
Incomplete outcome data (attrition bias)	Low risk	3 participants were withdrawn during the treatment period (1 from 100 µg group and 2 from 200 µg group) but all were included in analyses up to the point of withdrawal in an ITT analysis
Selective reporting (reporting bias)	Low risk	No protocol available. Most outcomes defined in the methods reported in the results (target joint rate bleeds mentioned in the methods but not in the results). The study is a Phase 2 dose ranging study so the main objective of the study is safety and pharmacokinetic measures, efficacy is a secondary measure so risk of bias is judged to be low
Other bias	Low risk	None identified

*Footnotes*

AICC: anti-inhibitor coagulant complex

AJBR: annualised joint bleeding rate

BU: Bethesda unit

FEIBA NF: nanofiltered factor eight inhibitor bypassing activity

HRQoL: health-related quality of life

ITI: immune tolerance induction

ITT: intention-to-treat

rFVIIa: recombinant factor VII

**Characteristics of excluded studies****NCT02622321**

Reason for exclusion	The study drug was not rFVIIa or APCC
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**NCT02795767**

Reason for exclusion	The study drug was not rFVIIa or APCC
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**NCT02847637**

Reason for exclusion	The study drug was not rFVIIa or APCC
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**NCT03020160**

Reason for exclusion	The study drug was not rFVIIa or APCC
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*Footnotes*

APCC: activated prothrombin complex concentrate

rFVIIa: recombinant factor VIIa

**Characteristics of studies awaiting classification****NCT01105546**



<b>Methods</b>	Multicenter parallel study in the USA, France, Germany, Italy, Romania and Spain
<b>Participants</b>	<p>Inclusion criteria: boys with hemophilia A who developed FVIII inhibitors, up to 8 years, <math>\leq 2</math> years from the time of inhibitor detection, high-responding inhibitor (<math>\geq 5</math> BU/mL) and known anamnestic response in case of negative inhibitor titre, candidate to start ITI with FVIII concentrates (doses ranging from 50 IU/kg/day to 200 IU/kg/day), <math>\leq 2</math> bleedings in the same joint within the last 6 months before entering the study, maximum 6 joint bleeds in the same joint within 2 years and adequate venous access</p> <p>Exclusion criteria: ITI already started, sensitivity to study drug, administration of study drug within 30 days prior randomization, family history of thrombosis at early age (<math>&lt; 40</math> years), known thrombophilia, any previous thrombosis, known pseudotumors, severe liver disease, platelet count <math>&lt; 50,000</math> platelet/<math>\mu</math>L and surgery within 1 month or planned for major surgery</p>
<b>Interventions</b>	<p>On demand: on-demand treatment, treatment of bleeding episodes with rFVIIa 270 <math>\mu</math>g/kg (first/single dose) or 90 <math>\mu</math>g/kg IV every 2-3 hours until bleeding resolution</p> <p>Prophylaxis: prophylaxis with rFVIIa 90 <math>\mu</math>g/kg/day</p>
<b>Outcomes</b>	No information provided
<b>Notes</b>	Study sponsored by Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico

*Footnotes*

ITI: immune tolerance induction

IU: international units

IV: intravenous

rFVIIa: recombinant factor VIIa

**Characteristics of ongoing studies***Footnotes***Summary of findings tables****1 Prophylaxis therapy compared with on-demand therapy with FEIBA for hemophilia A or B with inhibitors**

Prophylaxis therapy compared with on-demand therapy with FEIBA for hemophilia A or B with inhibitors						
<b>Population:</b> adults and children with hemophilia A or B with inhibitors						
<b>Settings:</b> outpatients						
<b>Intervention:</b> prophylaxis therapy (FEIBA)						
<b>Comparison:</b> on-demand therapy (FEIBA)						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	On-demand	Prophylaxis				
<b>Overall bleeding rates: total number of bleeding events</b> Follow-up: 6 months	Not estimable (see comment)	The mean total number of bleeding events in the prophylaxis group was <b>7.27 lower</b> than the on-demand group (9.92 lower to 4.62 lower).	Not estimable (see comment)	26 (1 study) <sup>1</sup>	⊕⊕⊕⊕ <b>low</b> <sup>2,3</sup>	Corresponding risk (mean difference between groups) was estimated taking account of the cross-over design of the study. Assumed risk in the on-demand group cannot be directly calculated.

<b>Annualised bleeding rate</b> Follow-up: 12 months	Median 28.7 (IQR, 32.3)	The median annualised bleeding rate was 7.9 (IQR 8.1), which was <b>72.5% lower</b> than on-demand group.	Not estimable (see comment)	34 (1 study)	⊕⊕⊕⊖ <b>moderate</b> <sup>2</sup>	Data presented as median values and could not be entered into analysis.
<b>Target joint bleeding rate: number of hemarthrosis</b> Follow-up: 6 months	Not estimable (see comment)	The mean number of hemarthrosis in the prophylaxis group was <b>6.60 lower</b> than the on-demand group (9.32 lower to 3.88 lower).	Not estimable (see comment)	26 (1 study) <sup>1</sup>	⊕⊕⊕⊖ <b>low</b> <sup>2,3</sup>	Corresponding risk (mean difference between groups) was estimated taking account of the cross-over design of the study. Assumed risk in the on-demand group cannot be directly calculated.
<b>AJBR</b> Follow-up: 12 months	Median 22.9 (IQR, 32.8)	The median AJBR was 6.0 (IQR 7.1), which was <b>73.8% lower</b> than on-demand group.	Not estimable (see comment)	34 (1 study)	⊕⊕⊕⊖ <b>moderate</b> <sup>2</sup>	Data presented as median values and could not be entered into analysis.
<b>Quality of life</b> Follow-up: 6 to 12 months	Not estimable (see comment)	There were also no significant differences between the prophylaxis and on-demand treatment for health-related quality of life.	Not estimable (see comment)	up to 58 (2 studies) <sup>1</sup>	⊕⊕⊕⊖ <b>low</b> <sup>2,3</sup>	The health-related quality of life was measured using Haem-A-QoL, Haemo-QoL, EQ-5D, and general pain visual analog scale (VAS) and the Short-Form (SF)-36 Health survey.
<b>Safety of bypassing agents</b> Follow-up: 6 to 12 months	Not estimable	There were no thromboembolic event and serious complications reported in participants who received treatment.	Not estimable (see comment)	up to 67 (2 studies) <sup>1</sup>	⊕⊕⊕⊖ <b>low</b> <sup>2,3</sup>	

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**AJBR**: annualised joint bleeding rate; **CI**: confidence interval; **FEIBA**: factor eight inhibitor bypassing activity; **IGR**: interquartile range

GRADE Working Group grades of evidence

**High quality**: further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality**: we are very uncertain about the estimate.

#### Footnotes

1. One study is of a cross-over design. 34 participants were randomized in the study but up to 24% of participants were excluded from results.

2. Downgraded once due to imprecision; limited information available from one or two small studies.

3. Downgraded once due to risk of bias: incomplete outcome data, up to 24% of participants are excluded from analyses.

## 2 High-dose compared with low-dose rFVIIa for hemophilia A or B with inhibitors

High-dose compared with low-dose rFVIIa for hemophilia A or B with inhibitors						
Population: adults and children with hemophilia A or B with inhibitors						
Settings: outpatients						
Intervention: high-dose therapy (rFVIIa)						
Comparison: low-dose therapy (rFVIIa)						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Low dose	High dose				
<b>Overall bleeding rates: number of bleeds per month</b> Follow-up: 3 months	The mean number of bleeds per month in the low-dose group was 2.18	The mean number of bleeds per month in the high-dose group was <b>0.82 lower</b> than the low-dose group (2.27 lower to 0.63 higher).	Not estimable	22 (1 study)	⊕⊕⊕⊖ <b>moderate</b> <sup>1</sup>	An additional study recruited participants to 200 µg/kg, 100 µg/kg and 25 µg/kg. Results showed reduction of overall bleeding rates for all 3 groups during prophylaxis as compared to on-demand period. (Data could not be entered into analysis as SDs not presented.)
<b>Annualised bleeding rate</b> Follow-up: 3 months	Not estimable (see comment)	Not estimable (see comment).	Not estimable (see comment)	24 (1 study)	NA	Results showed reduction of overall bleeding rates for all 3 groups during prophylaxis as compared to on-demand period. (Data could not be entered into analysis as SDs not presented.)
<b>Target joint bleeding rate</b> Follow-up: 3 months	The mean number of joint bleeds per month in the low-dose group was 4.7	The mean number of bleeds per month in the high-dose group was <b>3.20 lower</b> than the low-dose group (7.23 lower to 0.83 higher).	Not estimable	22 (1 study)	⊕⊕⊕⊖ <b>moderate</b> <sup>1</sup>	
<b>AJBR</b> Follow-up: 3 months	Outcome not reported.				NA	
<b>Quality of life</b> Follow-up: NA	Outcome not reported.				NA	
<b>Safety of bypassing agents</b>	There were no significant differences between doses in terms of adverse events or serious adverse events (see comment).		Not estimable	46 (2 studies)	⊕⊕⊕⊖ <b>moderate</b> <sup>1</sup>	Doses compared were: 270 µg/kg and 90 µg/kg 200 µg/kg and 100 µg/kg 200 µg/kg and 25 µg/kg 100 µg/kg and 25 µg/kg.
*The basis for the <b>assumed risk</b> is the event rate in the control group. The <b>corresponding risk</b> (and its 95% confidence interval) is based on the assumed risk in the comparison group and the <b>relative effect</b> of the intervention (and its 95% CI). <b>AJBR</b> : annualised joint bleeding rate; <b>CI</b> : confidence interval; <b>NA</b> : not applicable; <b>rFVIIa</b> : recombinant factor VIIa; <b>SD</b> : standard deviation						
GRADE Working Group grades of evidence <b>High quality</b> : further research is very unlikely to change our confidence in the estimate of effect. <b>Moderate quality</b> : further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. <b>Low quality</b> : further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. <b>Very low quality</b> : we are very uncertain about the estimate.						

## Footnotes

1. Downgraded once due to imprecision; limited information available from one or two small studies.

## Additional tables

## References to studies

### Included studies

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[CRSSTD: 6733042]

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Antunes SV, Tangada S, Phillips J, Stasyshyn O, Mamonov V, Guzman-Becerra N, et al. Comparison of historic on-demand versus prospective on-demand and prophylaxis bleeding episodes in hemophilia A and B patients with inhibitors treated with FEIBA NF. *Haemophilia* 2014;20:96. [CENTRAL: 1063882; CRS: 5500050000000504; CRSREF: 6733044; EMBASE: 71475655]

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#### **Konkle 2007**

[CRSSTD: 6733050]

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Konkle B, Friedrich U, Abrams Z. Secondary prophylactic treatment with rFVIIa in patients with haemophilia A or B and inhibitors with high requirements for on-demand treatment. *Haemophilia* 2006;12(Suppl 2):14. [Abstract no: PO363; CENTRAL: 593037; CRS: 5500100000002995; CRSREF: 6733052]

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[CRSSTD: 6733056]

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NCT00951405. Safety and efficacy of 3 different doses of long acting factor VII in haemophilia A or B patients with inhibitors [An exploratory multi-Centre, multi-national, randomised, double blinded, parallel arm trial evaluating safety, pharmacokinetics and dose-finding of prophylactic administration of long acting rFVIIa (LA-rFVIIa) in haemophilia A or B patients with inhibitors]. [clinicaltrials.gov/ct2/show/NCT00951405](http://clinicaltrials.gov/ct2/show/NCT00951405) Date first received: 03 August 2009. [CRSREF: 6733071]

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### **NCT02622321**

[CRSSTD: 6733072]

NCT02622321. A study to evaluate the efficacy, safety, and pharmacokinetics of prophylactic emicizumab versus no prophylaxis in hemophilia A patients with inhibitors (HAVEN 1) [A randomized, multicenter, open-label, phase III clinical trial to evaluate the efficacy, safety, and pharmacokinetics of prophylactic emicizumab versus no prophylaxis in hemophilia A patients with inhibitors]. [clinicaltrials.gov/ct2/show/NCT02622321](http://clinicaltrials.gov/ct2/show/NCT02622321) Date first received: 02 December 2015. [CRSREF: 6733073]

### **NCT02795767**

*Unpublished data only* [CRSSTD: 6733074]

NCT02795767. A study of once-weekly emicizumab in children and adolescents with hemophilia A and Factor VIII (FVIII)

inhibitors (HAVEN 2) [A single-arm, multicenter, open-label, phase III clinical trial to evaluate the efficacy, safety, and pharmacokinetics of once weekly subcutaneous administration of emicizumab in hemophilia A pediatric patients with inhibitors]. [clinicaltrials.gov/ct2/show/NCT02795767](https://clinicaltrials.gov/ct2/show/NCT02795767) Date first received: 07 June 2016. [CRSREF: 6733075]

### **NCT02847637**

*Unpublished data only [CRSSTD: 6733076]*

NCT02847637. A clinical trial to evaluate the efficacy, safety, and pharmacokinetics of prophylactic emicizumab versus no prophylaxis in hemophilia A participants without inhibitors (HAVEN 3) [A randomized, multicenter, open-label, phase III clinical trial to evaluate the efficacy, safety, and pharmacokinetics of prophylactic emicizumab versus no prophylaxis in hemophilia A patients without inhibitors]. [clinicaltrials.gov/ct2/show/NCT02847637](https://clinicaltrials.gov/ct2/show/NCT02847637) Date first received: 26 July 2016. [CRSREF: 6733077]

### **NCT03020160**

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*[CRSSTD: 6733080]*

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## **Other published versions of this review**

## **Classification pending references**

## **Data and analyses**

### **1 Prophylaxis compared to on-demand anti-inhibitor coagulant complex (AICC) or factor eight inhibitor bypassing activity (FEIBA NF)**

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 <a href="#">Overall bleeding rates: total number of bleeding events</a>	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.1.1 at 6 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.2 <a href="#">Overall bleeding rates: number of monthly bleeding events</a>	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.2.1 up to 6 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.3 <a href="#">Target joint bleeding rate: number of hemarthroses</a>	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.3.1 at 6 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.4 <a href="#">Target joint bleeding rate: number of joint hemorrhages</a>	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.4.1 at 6 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.5 <a href="#">Health-related QoL: change from baseline in total Haem-A-QoL score</a>	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.5.1 at 12 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.6 <a href="#">Health-related QoL: change from baseline in total EQ-5D score</a>	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.6.1 at 6 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.6.2 at 12 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals



1.7 <a href="#">Health-related QoL: change from baseline in EQ-5D VAS score</a>	2		Mean Difference(IV, Fixed, 95% CI)	Subtotals only
1.7.1 at 6 months	2	58	Mean Difference(IV, Fixed, 95% CI)	4.11 [-3.66, 11.88]
1.7.2 at 12 months	1	25	Mean Difference(IV, Fixed, 95% CI)	9.90 [-5.93, 25.73]
1.8 <a href="#">Health-related QoL: change from baseline in EQ-5D Utility score</a>	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.8.1 at 6 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.9 <a href="#">Health-related QoL: change from baseline in SF 36 Physical Functioning Score</a>	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.9.1 at 6 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.10 <a href="#">Health-related QoL: change from baseline in SF 36 Physical Score</a>	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.10.1 at 6 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.11 <a href="#">Health-related QoL: change from baseline in SF 36 Bodily Pain Score</a>	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.11.1 at 6 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.12 <a href="#">Health-related QoL: change from baseline in SF 36 General Health Score</a>	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.12.1 at 6 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.13 <a href="#">Health-related QoL: change from baseline in SF 36 Vitality / Energy Score</a>	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.13.1 at 6 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.14 <a href="#">Health-related QoL: change from baseline in SF 36 Social Functioning Score</a>	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.14.1 at 6 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.15 <a href="#">Health-related QoL: change from baseline in SF 36 Emotional Score</a>	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.15.1 at 6 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.16 <a href="#">Health-related QoL: change from baseline in SF 36 Mental Health Score</a>	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.16.1 at 6 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.17 <a href="#">Health-related QoL: change from baseline in SF 36 Physical Summary Score</a>	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.17.1 at 6 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.18 <a href="#">Health-related QoL: change from baseline in SF 36 Mental Summary Score</a>	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.18.1 at 6 months	1		Mean Difference(IV, Fixed, 95% CI)	No totals

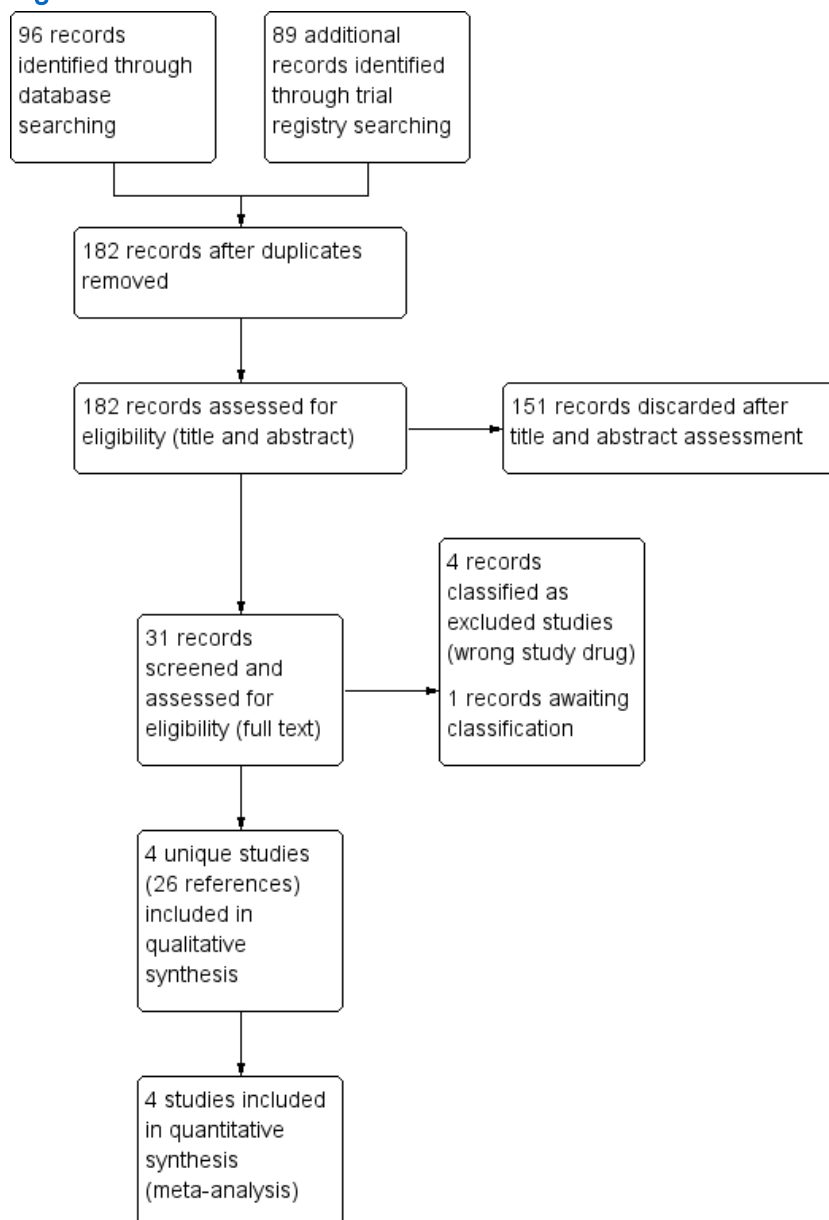
## 2 High-dose compared to low-dose recombinant factor VIIIa (rFVIIIa)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 <a href="#">Overall bleeding rates: number of bleeds per month</a>	1		Mean Difference(IV, Fixed, 95% CI)	No totals
2.2 <a href="#">Target joint bleeding rate: number of joint bleeds over 3 months</a>	1		Mean Difference(IV, Fixed, 95% CI)	No totals

2.3 Number of adverse events	2		Risk Ratio(M-H, Fixed, 95% CI)	No totals
2.3.1 200 µg/kg vs 100 µg/kg	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
2.3.2 200 µg/kg vs 25 µg/kg	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
2.3.3 100 µg/kg vs 25 µg/kg	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
2.3.4 270 µg/kg vs 90 µg/kg	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
2.4 Number of serious adverse events	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals

## Figures

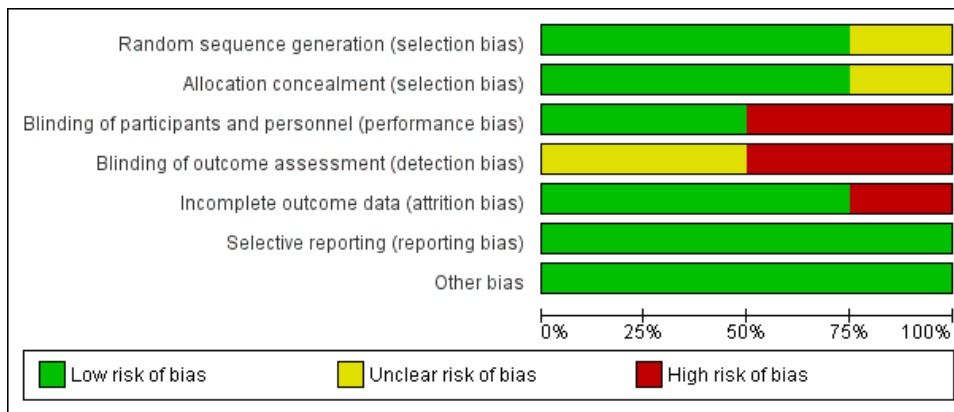
Figure 1



### Caption

Study flow diagram.

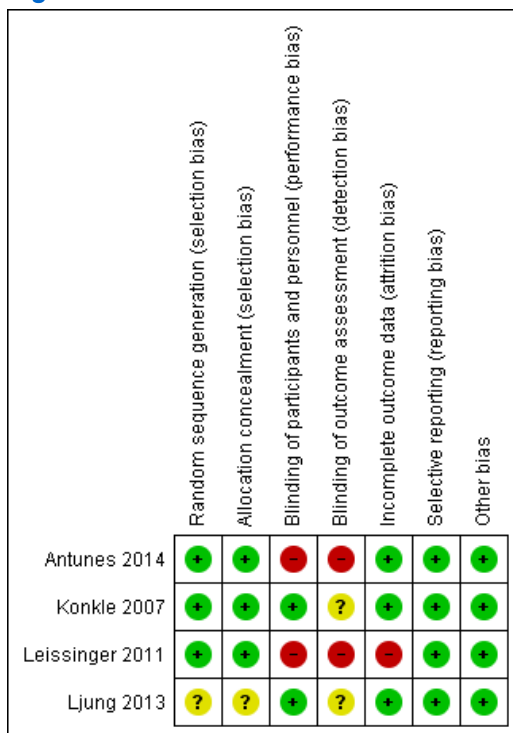
Figure 2



### Caption

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

### Figure 3



### Caption

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

## Sources of support

### Internal sources

- No sources of support provided

### External sources

- National Institute for Health Research, UK  
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## Feedback

## Appendices

### 1 Online trials databases - search strategies

#### Clinicaltrials.gov

Advanced Search Form

Search terms: haemophilia AND inhibitor AND prophylaxis

Study type: Interventional Studies

**WHO ICTRP**

Advanced Search Form

Condition: inhibitor\* AND haemophilia\* OR hemophilia\*

Intervention: prophyla\*

[Recruitment status: ALL]